Remarks

The Office Action mailed January 31, 2006 has been received and reviewed. Claims 13-16, 18-24, 27-32, 34, and 35 having been cancelled and claims 2-4, 6, 7, 17, 25, 26, and 33 having been amended, the pending claims are claims 1-12, 17, 25, 26, and 33. Claims 10 and 11, drawn to the invention of Group V, are currently under examination. Applicants respectfully submit that claims 2-7, 17, 25, 26, and 33, as amended, are also drawn to the invention of Group V. The rejoinder and examination of claims 2-7, 17, 25, 26, and 33 along with claims 10 and 11 is requested. Reconsideration and withdrawal of the rejections are respectfully requested.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 10 and 11 under 35 U.S.C. §103 as being unpatentable over Ito et al. (Oncology (2001) 61:221-225) in view of Massague et al. (International Publication No. WO 96/31534) and in further view of Allen-Hoffman et al. (U.S. Patent No. 6,214,567). This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. See MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the references when combined must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully submit that the Examiner has failed to establish these basic requirements of a *prima facie* case of obviousness in the rejection of claims 10 and 11 under 35 U.S.C. §103(a) as being unpatentable over Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al.

Claim 10 is drawn to "[a] method of determining the therapeutic effectiveness of an agent, the method comprising:

contacting normal cells with the agent;

determining the p57/KIP2 level in the normal cells after contacting with the agent;

contacting cancer cells with the agent;

determining the p57/KIP2 level in the cancer cells after contacting with the agent;

and

comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent;

wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer." Claim 11 is drawn to "[t]he method of claim 10, wherein the normal cells and cancer cells are cultured together."

Thus, in the method of claims 10 and 11, two separate cell populations are each contacted with the agent; both normal cells are contacted with the agent and cancer cells are contacted with the agent. Further, in the method of claims 10 and 11, "the p57/KIP2 level in the normal cells after contacting with the agent" is compared to "the p57/KIP2 level in the cancer cells after contacting with the agent." And, in the method of claims 10 and 11, "a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer." Applicants note that "P57/KIP2" is also referred to as "p57," "p57(Kip2)" and "$p57^{KIP2}$" in the various documents cited by the Examiner.

The teachings of Ito et al.

Ito et al. "studied the expression of p57 in a large number of HCC [hepatocellular carcinomas] in order to elucidate the clinical significance of this protein" (see page 22, col. 1). Ito et al. "investigated the expression of p57 (Kip2) in 90 hepatocellular carcinomas and 66 noncancerous lesions" (see abstract) and "found that p57 expression was significantly decreased . . . in heptocellular carcinoma" and "was significantly lower in heptaocellular carcinoma cases

with high biological aggressiveness" (see abstract). "Furthermore, cases with low p57 expression showed worse outcomes for disease-free survival . . . although p57 expression could not be recognized as an independent prognostic factor" (see abstract). Thus, the teachings of Ito et al. note decreased expression of p57/KIP2 in cancerous heptaocellular cells compared to noncancerous cells and note a correlation between decreased p57/KIP2 expression and aggressiveness of the cancerous cells (See "Discussion," pages 223-224).

The teachings of Massague et al.

Massague et al. teach "a method of determining whether an agent is capable of specifically inhibiting the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex" (page 5, lines 16-18); "a method of determining whether an agent is capable of specifically enhancing the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex" (page 5, lines 33-35); and methods of treating a subject having a hyperproliferative disorder by administering "a therapeutically effective amount of an agent capable of specifically enhancing the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex in the hyperproliferative cells of the subject" (page 6, lines 14-18) or administering "a therapeutically effective amount of an agent capable of specifically inhibiting the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex in the hyperproliferative cells of the subject" (page 6, lines 22-26). Thus, Massague et al. teach methods for the determination of therapeutic agents that inhibit or enhance the "the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex."

And while Massague et al. teach methods "for quantitatively determining the amount of $p57^{KIP2}$ in a sample" (see, for example, page 28, lines 23-31) and "for determining whether an agent is capable of increasing or decreasing the level of expression of $p57^{KIP2}$ in a cell population" (page 29, lines 12-14), Applicants respectfully submit that the Examiner's assertion that "Massague et al. further teach (page 29, lines 10-24) screening for therapeutic agents that are capable of increasing or decreasing the level of expression of p57/KIP2" (page 4 of Office Action mailed January 31, 2006) is incorrect. Applicants submit that Massague et al. teach

screening only for therapeutic agents capable of either inhibiting or enhancing "the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex." Applicants submit that Massague et al. does not teach therapeutic agents that are capable of increasing or decreasing the level of expression of p57/KIP2 or methods of screening for such therapeutic agents.

The teachings of Allen-Hoffmann et al.

Allen-Hoffmann et al. teach an immortalized human keratinocyte cell line (see, for example, abstract and col. 2, lines 19-21). This immortalized human keratinocyte cell line "has the substantial advantage of reproducing the tissue architecture of normal human stratified squamous epithelia" (col. 4, lines 24-26) and Allen-Hoffmann et al. teach a method of creating a reconstructed epidermis by co-culturing immortalized keratinocyte cells along with human malignant squamous epithelial cells (SCC) (see, for example, abstract and col. 2, lines 30-38). The immortalized human keratinocyte cells "provide a reproducible environment in which to compare the growth characteristics of SCC cells" (col. 4, lines 24-31 and 49-53) and Allen-Hoffmann et al. teach a method of "screening drugs or agents used in the treatment of cancers of stratified squamous epithelia" (col. 4, lines 37-39 and claim 1). "One . . . treats the [reconstructed] epidermis with a test tumor cell modulating agent and evaluates the growth of the malignant cells within the [reconstructed] epidermis" (abstract). Thus, while Allen-Hoffmann et al. teach co-culturing two separate populations of cells, Allen-Hoffmann et al. do not teach determining the response of each of the two separate cells populations after contact with an agent.

Requisite motivation to combine documents is absent

According to MPEP § 2143.01, "[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art."

Applicants respectfully submit that the requisite motivation to combine the teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. is not found either in the teachings of Ito et al., Massague et al., or Allen-Hoffman et al. themselves or in the knowledge generally available to one of ordinary skill in the art.

Applicants submit that one of ordinary skill in the art would not be motivated to combine the teachings of Ito et al. (noting a decreased expression of p57KIP2 in cancerous heptaocellular cells compared to noncancerous cells and a correlation between decreased p57KIP2 expression and aggressiveness of the cancerous cells) with the teachings of Massague et al. (screening for therapeutic agents capable of either inhibiting or enhancing "the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex") to obtain the present invention: a method comprising contacting both normal cells and cancer cells with an agent; "comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent; wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer."

The Examiner asserted that "[o]ne would have been motivated to combine the teachings because it was well known in the art, at the time the invention was made, to determine the therapeutic effectiveness of an agent by comparing the levels of p57/KIP2 in normal and cancer cells because Massague et al. teach (page 6, lines 27-32) that a lesser amount of active cyclin-CDK complex formed in the presence of an agent than in the absence of the agent indicate that the agent is capable of specifically enhancing the ability of p57/KIP2 to inhibit the activation of cyclin-CDK complex" (page 4, Office Action mailed January 31, 2006). Applicants adamantly disagree. Applicants submit that the Examiner's assertion that "it was well known in the art, at the time the invention was made, to determine the therapeutic effectiveness of an agent by comparing the levels of p57/KIP2 in normal and cancer cells" (page 4, Office Action mailed January 31, 2006) is incorrect. Massague et al. provides no such teachings; Massague et al. teach only therapeutic agents that either enhance or inhibit "the ability of p57/KIP2 to inhibit the activation of cyclin-Cdk complex formation (see page 6, lines 14-28). Further, Applicants

submit that the combined teachings of Ito et al. and Massague et al. provide no motivation for the method of the claimed invention, "wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer."

Likewise, Applicants respectfully submit that one of ordinary skill in the art would not be motivated to further combine the teachings of Ito et al. (noting decreased expression of p57KIP2 in cancerous heptaocellular cells compared to noncancerous cells) and Massague et al. (screening for therapeutic agents that inhibit or enhance "the ability of $p57^{KIP2}$ to inhibit the activation of cyclin-Cdk complex") with the teachings of Allen-Hoffman et al. (co-culturing immortalized keratinocyte cells along with human malignant squamous epithelial cells to form a reconstructed epidermis for use in screening for agents useful in the treatment of cancers of stratified squamous epithelia) to obtain the present invention.

The Examiner asserted that "it can be advantageous to screen agents by using p57/KIP2 in co-cultures because Allen Hoffmann et al. teach (col.5, lines 54+) that such co-cultures are useful for: (1) screening for novel cytostatic inhibitors of tumor repopulation, (2) determining patient-specific responses to chemotherapy or radiotherapy prior to treatment, and (3) developing novel, biologic therapeutic agents" (pages 4-5 of Office Action mailed January 31, 2006). Applicants do not understand this statement. Applicants submit that, while the reconstructed epidermis taught by Allen-Hoffmann et al., formed by co-culturing immortalized keratinocyte cells along with malignant squamous epithelial cells, "may be useful for at least three critical problems faced by the pharmaceutical and biotechnology industries" (see col. 5, lines 54-60 of Allen-Hoffmann et al.), these teachings of Allen-Hoffmann et al. do not provide motivation to combine the disparate teachings of Ito et al., Massague et al., and Allen Hoffman et al.

The Examiner asserted that "[o]ne of ordinary skill in the art would have reasonably expected to obtain a benefit upon combining Ito's with Massague's and Allen-Hoffmann's teachings because the combined teachings had been demonstrated in the prior art to be

reasonably predictive of screening for therapeutic agents" (pages 4-5 of Office Action mailed January 31, 2006). Applicants do not understand this statement and request the Examiner provide copies of the referenced "***prior art***" that "***demonstrates***" that the combined teachings of Ito et al. in view of Massague et al. and further in view of Allen-Hoffmann et al. are ***"reasonably predictive of screening for therapeutic agents."***

Applicants respectfully submit that the requisite motivation to combine the teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al., to arrive at the claimed invention, is absent. Applicants submit that claims 10 and 11 are not *prima facie* obvious over Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. Reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) is requested.

No reasonable expectation of success

According to MPEP § 2143.02, "[t]he prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants submit that one of ordinary skill in the art would not have a reasonable expectation of success in combining the disparate teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. Rather, Applicants submit that the combined teachings, and in particular, the teachings of Ito et al. (correlating *decreased* p57KIP2 expression with *increased* tumor aggressiveness and showing that "low p57 expression showed worse outcomes for disease-free survival" (see abstract)), teach away from the methods of the present invention. From the teachings of Ito et al., that low p57 expression in cancer cells correlates with worse outcomes for disease-free survival, one would not have a reasonable expectation of success in combining the teachings Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. to obtain the claimed method, "wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer."

Thus, Applicants submit that claims 10 and 11 are not *prima facie* obvious over Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. Reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) is requested.

Documents combined do not teach the claimed invention

According to MPEP § 2143.03, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)." Applicants submit that the teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. do not teach each and every element of the claimed invention.

Specifically, claims 10 and 11 are drawn to a "method of determining the therapeutic effectiveness of an agent . . . wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer." Applicants respectfully submit that the combined teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. do not teach or suggest such a "method of determining the therapeutic effectiveness of an agent . . . wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer," as recited in claims 10 and 11.

Further, the method of claims 10 and 11 comprises:

"*contacting* normal cells with the agent;

determining the p57/KIP2 level in the normal cells after contacting with the agent;

contacting cancer cells with the agent;

determining the p57/KIP2 level in the cancer cells after contacting with the agent; and

comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent."

Applicants respectfully submit that the combined teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. do not teach or suggest a method comprising all

of these method steps. Specifically, the combined teachings do not teach or suggest a method comprising "*contacting* normal cells with the agent," "*determining* the p57/KIP2 level in the normal cells after contacting with the agent," "*contacting* cancer cells with the agent, "*determining* the p57/KIP2 level in the cancer cells after contacting with the agent," and "*comparing* the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent," as recited in claims 10 and 11.

Further, the method of claims 10 and 11 comprises "contacting *normal cells* with the agent; *determining the p57/KIP2 level in the normal cells* after contacting with the agent; . . . and comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent." Applicants respectfully submit that the teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. do not teach or suggest a method including all of these various method steps pertaining to normal cells. Specifically the combined teachings do not teach "contacting normal cells with the agent," "determining the p57/KIP2 level in the normal cells after contacting with the agent," and "comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent," as recited in claims 10 and 11.

Finally, the method of claims 10 and 11 comprises "contacting *cancer cells* with the agent; *determining the p57/KIP2 level in the cancer cells* after contacting with the agent; and comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent." Applicants respectfully submit that the teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. do not teach or suggest a method including all of these various method steps pertaining to cancer cells. Specifically the combined teachings do not teach "*contacting* cancer cells with the agent; *determining* the p57/KIP2 level in the cancer cells after contacting with the agent; and *comparing* the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2

level in the cancer cells after contacting with the agent," as recited in claims 10 and 11.

Thus, Applicants submit that Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. do not teach each and every element of the method of claims 10 and 11. Claims 10 and 11 are not *prima facie* obvious over Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. Reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) is respectfully requested.

Conclusion

In conclusion, Applicants respectfully submit that the requisite motivation to combine the teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. is absent. Further, Applicants respectfully submit that there is not a reasonable expectation of success in combining the teachings of Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. Finally, Applicants submit that Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. do not teach every element of the claimed method. Thus, the Examiner has failed to establish the basic requirements of a *prima facie* case of obviousness in the rejection of claims 10 and 11 as being unpatentable over Ito et al. in view of Massague et al. and in further view of Allen-Hoffman et al. Reconsideration and withdrawal of this rejection of claims 10 and 11 under 35 U.S.C. §103(a) is respectfully requested.

Amendment and Response
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Summary

It is respectfully submitted that the pending claims 2-7, 10, 11, 17, 25, 26, and 33 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

CERTIFICATE UNDER 37 C.F.R. 1.8:

The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 25 day of April, 2006, at 2:20 pm (Central Time).

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